UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 22, 2019

MEMORANDUM

SUBJECT: Ethics Review of Completed AHETF Study AHE500 on Worker Exposure during Closed System Loading of Liquids

FROM: Michelle Arling, Human Research Ethics Review Officer
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TO: Dana Vogel, Director
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REF: Bruce, Eric D. (2019) Determination of Dermal and Inhalation Exposure to Workers during Closed System Loading of Liquids in Returnable and Non-Returnable Containers. Study Number AHE500, 1386 p., April 24, 2019. (MRID 50846201)

Bruce, Eric D. and Holden, Larry R. (2019) Agricultural Handler Scenario Monograph: Mechanical Transfer of Liquids. Report Number AHE1022, 311 p., Draft Report. April 30, 2019. (MRID 50940301)

Bruce, Eric D. (2019) IRB Correspondence Report for Study AHE500. Related Submissions: Study Report AHE500 and Scenario Monograph Report No. AHE1022. 891 p., April 23, 2019.

I have reviewed the available information concerning the ethical conduct of the research reported by the Agricultural Handler Exposure Task Force (AHETF) in the referenced documents. The documents describe the implementation and results of a field study, the objective of which was to develop data to determine the potential dermal and inhalation exposure for workers who loaded liquid pesticides packaged in either returnable or non-returnable containers into "closed systems." The monograph report summarizes the dermal and inhalation exposure data collected through study AHE500, as well as data from other exposure monitoring research conducted before the implementation of EPA's Human Studies rule (40 CFR 26). The IRB correspondence report presents, in chronological order, the ethics-related documentation for study AHE500, including but not limited to submissions to and approval from the IRB, amendments to and deviations from the protocol, consent and recruitment documents, and written communications between the study sponsor and the overseeing IRBs.

Based on the information available, study AHE500 met applicable ethical standards for the protection of human subjects of research, and the complete submission satisfied the requirements for

documentation of ethical conduct of the research. Therefore, if study AHE500 and scenario monograph report AHE1022 are determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on them in actions under FIFRA or §408 of FFDCA.

In addition, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's Human Studies rule that are initiated after April 7, 2006. This review covers only the ethical conduct of study AHE500, which was initiated after EPA's Human Studies rule went into effect and requires review by the HSRB prior to EPA's reliance on the research. The monograph report (AHE1022) includes information about other worker exposure monitoring studies submitted to EPA that were conducted prior to the effective date of EPA's Human Studies rule, and therefore do not require review by the HSRB. EPA will share study AHE500, scenario monograph report AHE1022, the associated support documents, and EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute EPA's ethics review of study AHE500.

Summary Characteristics of the Research

Study AHE500's objective was to develop data to characterize the potential exposure of workers who loaded liquid pesticides into closed systems using two types of containers – returnable containers (intended to be returned to the manufacturer following use or refilled from a bulk loading tank) and non-returnable containers (single-use containers, usually rinsed in the field and recycled or destroyed). The dermal and inhalation exposure information was collected from workers conducting loading tasks with these types of containers while wearing inner dosimeters (long underwear) under regular work clothes and air sampling pumps. In addition, researchers collected face and hand wipe samples from the subjects at the end of the workday, and as necessary at other points during the monitoring. Although the protocol was designed to collect exposure data related to each type of container separately, the exposure between workers loading pesticides into closed systems from non-returnable and returnable containers did not differ significantly, so all data were analyzed together. For a complete discussion of the rationale for analyzing the scenarios together, see the report "Closed System Liquid Loading (CSLL) Rationale for a Single Monograph: Mechanical Transfer of Liquids (MTL)" dated October 7, 2019 and prepared by AHETF.

The protocol noted that "[c]losed systems utilized must be designed to enclose the pesticide to prevent it from contacting handlers while liquids are transferred from containers to mixing or application tanks." (AHE500 Study Report, p. 474 of 1386) Four types of closed systems were considered: suction/extraction systems, container breach systems, gravity-fed systems, and other systems such as direct injection or glove boxes. (Id.) The protocol recognized that in some instances what a grower considered a closed system might not be completely closed or involve totally secure connection, but allowed these types of systems to be included in the study as they represented real-world scenarios and "they still minimize[d] contact during the transfer of the liquid." (Id.)

A monitoring unit or MU refers to a single subject (worker) who is carrying out activities using a particular pesticide formulation under a specific scenario, on a particular day. For each MU in this study, the protocol called for subjects transfer liquid pesticides using a closed system to prepare at least 3 loads. Monitoring lasted from 1.2 hours to 8.9 hours, and generally reflected a typical workday for the subjects being monitored. MUs also included other non-study work-related tasks, as well as breaks. Every MU provides an estimate of a single handler-day of exposure to the worker through measurement of the dermal and inhalation exposure potential for a single subject for a time period that represents a typical workday. A cluster is a group of MUs that are performed close together in terms of location and time. The AHE500 protocol, approved by Independent Investigational Review Board (IIRB), specified 36 MUs to be conducted, 21 with workers using non-returnable containers and 15 with workers using returnable containers. For workers using non-

returnable containers, the MUs were to be collected across 7 geographic areas. For workers using returnable containers, the MUs were to be collected across 5 geographic areas. There was overlap in the geographical areas for each scenario. The protocol was amended to allow the final 3 MUs to be collected in any monitoring area. (AHE500 Study Report, pp. 494-500 of 1386; Amendment 3) In the course of the study, a total of 21 MUs were conducted with workers using non-returnable containers, and 15 were conducted with workers using returnable containers. Two MUs from the non-returnable container scenario were invalidated after they were conducted. MU23 was invalidated for lack of valid analytical result for one inner dosimeter piece and one section of the OVS tube. MU2 was invalidated "because the subject used spray mixture to rinse the jugs, created a spill by leaving the rinse valve open while the jug was removed, and did not clean up the spill with extra clothing/PPE." (AHE500 Study Report, p. 102 of 1386) The first MU for this study was conducted in November 2012 and the last MU was conducted in September 2016.

The tables below identify the monitoring areas for the 36 MUs by container type, and the number of workers/MUs per monitoring area.

Closed System Loading of Liquids – Non-Returnable Containers

Monitoring Area Number/ID Code	State Included in Monitoring Area	Monitoring Units Conducted
501	Arizona (Colorado)	3
502	Florida (Georgia, South Carolina)	3
503	Michigan (Wisconsin)	3
504	Nebraska	3
505	Washington State	3
506	Mississippi	3
507	Texas (Arkansas, Louisiana)	3

Closed System Loading of Liquids – Returnable Containers

Monitoring Area Number/ID Code	State Included in Monitoring Area	Monitoring Units Conducted
511	Arizona (Colorado)	3
512	Florida	3
513	Michigan	3
514	Nebraska	3
515	Washington State (Oregon)	3

The original IRB-approved protocol specified that monitoring should be conducted in the first state listed, but allowed the Study Director to "[e]xpand the monitoring area by incorporating a new geographic area adjacent to the original monitoring area." (AHE500 IRB Correspondence Report, p. 201 of 891). The states listed in parentheses are those added during the course of the study, expanding the monitoring area to ensure the requisite number of MUs could be collected.

Required Reviews of Protocol and Ethics-Related Chronology

A draft of the protocol for study AHE500 was submitted to the Independent Investigational Review Board, Inc. (IIRB) on July 8, 2011 and approved on July 13, 2011. AHETF submitted the

IIRB-approved protocol and associated materials to EPA. The HSRB discussed the protocol and EPA's scientific and ethics review[1], dated September 26, 2011, at a meeting on October 20, 2011, and responded with support for the study to move forward after the AHETF addressed comments from EPA and the HSRB. With regard to ethics, the HSRB's final meeting report concluded "that the protocol submitted for review, if modified in accordance with EPA and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L."[2] The AHETF made revisions based on feedback from EPA and HSRB, submitted the revised documents to IIRB on February 17, 2012 and received approval on February 22, 2012 (AHE500 IRB Correspondence Report, pp. 165-274 of 891). A summary of EPA's and HSRB's recommendations and how the AHETF addressed them is included in Attachment 1.

Oversight of the protocol was handled initially by IIRB. On October 24, 2012, the AHETF was notified that as of October 1, 2012, IIRB "was absorbed into its parent company Schulman Associates Institutional Review Board, Inc." (AHE500 IRB Correspondence Report, pp. 383-4 of 891). Subsequent review of study AHE500 was performed by Schulman IRB #3. On March 5, 2018, SAIRB notified the AHETF that the Chesapeake IRB and SAIRB merged to created Advarra (AHE500 IRB Correspondence Report, pp. 841-2 of 891). On July 25, 2018, oversight of the study wasn transferred to Advarra; at this point, all MUs had been completed and the study was open for analysis only. Advarra approved close out of the study on April 19, 2019.

All three IRBs involved in the oversight of this study were registered with the Office of Human Research Protections, held a federal-wide assurance, and were accredited by the Association for the Accreditation of Human Research Protection Programs. Necessary documentation for each of the IRBs involved in review of this study were provided to EPA. A summary of the ethics-related protocol amendments and deviations is included below.

Completeness of Submission

The checklist used by EPA to verify fulfillment of the requirements of §26.1303 as they apply to this research is provided in Attachment 2.

Grower Recruitment

With regard to recruitment of growers, the protocol references SOPs 11.K., 11.L, and 11.M. The recruitment process outlined in the protocol and these SOPs appears to have been followed in study AHE500.

According to the protocol and completed study report, recruitment activities occurred in three phases, summarized as follows:

- Phase 1: Create Universal List from commercial grower lists and commercial applicator companies in the monitoring area. Employ professional call center to determine whether they use closed systems to transfer liquids from returnable and/or non-returnable containers; those that do are included in the Qualified List. Also contact local experts and the National Agricultural Aviation Association to identify potentially eligible employers, confirm they use closed systems, and get permission to share their information with AHETF. Add potential participants identified through local experts directly to the Qualified List (no contact by the call center).

[1] Evans, J., Sarkar, B., and Sherman, K. Science and Ethics Review of AHETF Scenario Design and Protocol AHE500 for Exposure Monitoring of Workers During Closed System Loading of Returnable and Non-Returnable Containers in the United States. September 26, 2011. https://archive.epa.gov/osa/hsrb/web/pdf/2a-ahetf-closed-loading-protocol.pdf

[2] Philpott, Sean. October 19-20, 2011 EPA Human Studies Review Board Meeting Report. January 11, 2012. https://archive.epa.gov/osa/hsrb/web/pdf/hsrb_meeting_final_report_for_october_2011-certified.pdf

- Phase 2: Work with Local Agricultural Specialists to identify additional potential employers who would be qualified and interested in participating and add them to the list. Send introductory letter and flyer to all entities on the Qualified List, briefly describing the study and notifying them they might receive about participation. Have a member of the research team contact all growers on the Qualified List to determine whether they agree to cooperate in the study, have the appropriate equipment, are willing to use an AHETF surrogate chemical, are willing to have employees participate in the study, and are willing to sign a non-coercion agreement. The researcher also collects information about the equipment and containers used, timing of application, products used, and employees. When growers who were qualified and tentatively agreed to participate were identified by researchers, their contact information was provided to the Study Director or his designee.
- Phase 3: Contact and visit potentially eligible employers, confirm their eligibility and then schedule and conduct monitoring of workers who volunteer and have the necessary qualifications. (AHE500 Study Report, p. 25 of 1386)

This process recruited potential subjects for both scenarios of this study. During the first phase, potential subjects were added to the list for the returnable scenario, the non-returnable scenario, or both, depending on what types of closed system loading activities their workers performed during Phase 1. During phase 2, this information was verified and, in some instances, updated to reflect the researcher's more complete understanding of the types of activities that occurred on the establishment. During phase 3, the report notes that "the AHETF Study Director (or a designee) made an effort to contact and/or visit Potentially Eligible Employers in order to locate growers that might participate in a timeframe and schedule to allow the monitoring to be conducted efficiently. Initial contacts were made by telephone. When promising situations arose (i.e., willing growers, suitable closed system, and researcher availability), arrangements were made to visit the growers, inspect their equipment, and recruit participants for the study." (AHE500 Study Report, p. 32 of 1386)

The table below is taken from page 27 of the AHE500 Study Report, and summarizes the numbers of monitoring units (MUs) for each monitoring area. The study report provides specific details about the recruitment details by monitoring area (AHE500 Study Report, pp. 24-75 of 1386)

Scenario	Monitoring Area	Employer Universe List	Qualified Employer List	Potentially Eligible Employer List	Eligible Employer List	MUs Collected
CSLL-NR	501 = AZ	1,529	112	15	5	3
	502 = FL	4,802	130	30	13	3
	503 = MI	7,651	171	20	5	3
	504 = NE	4,686	168	30	10	3
	505 = WA	700	77	15	5	3
	506 =MS	766	81	40	10	3
	507 = TX	5,564	152	39	9	3
CSLL-R	511 = AZ	1,529	116	36	8	3
	512 = FL	628	70	23	15	3
	513 = MI	1,140	96	34	4	3
	514 = NE	4,686	192	57	14	3
	515 = WA	2,080	116	41	12	3

A poll of agricultural experts conducted in each monitoring area after all MUs for Study AHE500 were completed was taken "to evaluate the representativeness of the equipment and operators used in the study to the general population of equipment and operators." (AHE500 Study Report, p. 76 of 1386) A total of 115 surveys were distributed and 38 were returned. Overall, the surveys returned to the AHETF indicated the experts' belief that the growers and their facilities were representative of the industry as a whole. Of the 38 surveys completed, only 3 indicated that the MUs were not representative. The 3 respondents who disagreed that the study was not representative of equipments and operators indicated that in their experience companies are a different size than those represented in this study.

Subject Recruitment and Consent

Subject recruitment, selection, and consenting were carried out according to the protocol and relevant SOPs (11.B., 11.C., 11.D., 11.J.). During the grower recruitment phase and prior to recruitment of subjects, employers signed a non-coercion statement (SOP 11.B.7; AHETF SOP Manual, p. 150 of 251) agreeing that they would not coerce or influence their employees' decision about whether to participate in the study and that workers' employment would not be affected regardless of their participation. They also agreed to provide alternate work for those employees who choose not to participate in the study. This step was not carried out when the owner was also the prospective subject.

Monitoring Area	Workers Attending Recruitment Meeting	Workers Attending a Consent Meeting	Workers Signing a Consent form	Workers Withdrawing After Consenting	Workers Monitored
501	4	4	4	0	3
502	3	3	3	0	3
503	4	4	4	0	3
504	3	3	3	0	3
505	4	4	4	0	3
506	7	4	4	0	3
507	6	5	4	0	3
511	5	5	5	0	3
512	4	4	4	0	3
513	5	5	5	0	3
514	4	4	4	0	3
515	4	4	4	0	3

Following the protocol and SOP-11.B., workers were recruited through meetings with research staff, without employers present (where applicable). The researchers provided the IRB-approved recruitment flyer and informed consent materials, either in advance or at the time of the recruitment and consent meeting. Researchers presented to the prospective subjects the information in the consent form, including the goals of the research study, the procedures used in exposure monitoring, and the risks and benefits to subjects. All interested and qualified subjects completed the consent process. In obtaining consent from each subject, the AHETF followed SOP-11.J. and the protocol. All meetings were held one-on-one between the researcher and the subject, in a private location where the discussion could not be overheard by anyone else. After reviewing the consent form and the product label (if available at the time of consent), and answering any questions, the researcher asked a series of questions (SOP-11.J; AHETF SOP Manual, p. 188-190 of 251) to confirm the subject's understanding of the materials covered prior to obtaining the subject's informed consent.

Materials and meetings were available in English and Spanish. The protocol noted that for subjects who preferred to conduct the meeting in Spanish, a bilingual researcher would be available on site both during the consent meeting and during the MU (see SOP 11.I); however, all subjects requested communications and materials in English.

Subjects met the inclusion criteria outlined in AHETF SOP 11.B. Subjects had experience handling pesticides as part of their job, were trained in safe pesticide handling procedures, provided proof that the were at least 18 years old, confirmed that they were not an employee of a pesticide company, were in good health and had no medical conditions that would affect their ability to participate in the study. Subjects confirmed that they usually wore the personal protective equipment (PPE) required by the label, and were willing to wear the long underwear/inner dosimeter. Subjects also met the study-specific criteria listed in the protocol:

- "Have experience within the past year with closed loading of liquids in returnable containers (CSLL-R) or with closed loading of liquids in non-returnable containers (CSLL-NR) including the type of equipment to be used." (AHE500 IRB Correspondence Report, p. 175 of 891)
- Agree to wear chemical-resistant gloves even if the label does not require them. (AHE500 IRB Correspondence Report, p. 184 of 891)

The AHETF verified the age of each subject by reviewing the subject's government-issued photo identification during the consent process. The female subject completed a pregnancy test on the day of her MU before monitoring began in accordance with the protocol requirements and was eligible to continue participation in the study.

Across the 7 monitoring areas, a total of 47 consented to participate. In most instances, only one worker was eligible and consented. In instances where more than one subject was qualified, available, and willing, the selection of the subject for monitoring was done randomly. Of the 36 subjects who completed MUs, 35 were male and 1 was female. Subjects ages ranged from 23 years old to 65 years old. The AHE500 Study Report includes additional information about the subjects who completed MUs on pp. 119-122 and 312-314.

Product-Specific Information for Subjects

The study followed the protocol requirements for ensuring that subjects received information about the specific products used and safety precautions to be taken while handling the test substance. The protocol and AHETF SOP-11.E called for providing each subject with the identity of the substance that he or she would be monitoring, in addition to reviewing a copy of the labeling and discussing required personal protective equipment (PPE) and potential health effects. Because the specific product to be used was selected by the grower, the product identity was not always known to the researchers at the time of the consent meeting. The protocol called for informing the subject during the consent process and prior to participation a copy of the label, and for reviewing with the subject the safety information from the label (risks, precautionary statements, requirement to use label-specified PPE, importance of washing hands prior to eating or smoking, and other safe pesticide handling practices). (AHE500 Study Report, p. 440 of 1386) All participating subjects were informed of the active ingredient and the end-use product before monitoring began, and field staff reviewed the label information with the subjects prior to participating in the study consistent with the protocol, SOP-11.E. and the informed consent form.

PPE and Work Clothing

The protocol called for subjects to wear the PPE required by the labeling. The protocol also noted that SOP 11.E. would be followed, which required researchers to monitor subjects'

compliance with the labeling requirements. A summary of the clothing and PPE worn by each subject can be found in tables CSLL-NR-5 and CSLL-R-5 of the AHE500 Study Report (pp. 119-122 and 312-314). Subjects participating in study AHE500 wore the PPE as specified on product labeling and in the approved protocol (i.e., chemical-resistant gloves). All subjects wore long-sleeved shirts and long pants or coveralls over the whole-body dosimeters provided by the AHETF. Most subject wore their own clothing; in a few instances, AHETF provided freshly-laundered long-sleeved shirts to subjects who arrived on the test day wearing short-sleeved shirts. The AHETF confirmed that all work clothing was laundered prior to the day of the MU. In addition, the AHETF provided the required chemical-resistant gloves worn by all participating workers. Subjects wore their own shoes and socks.

Heat Stress Monitoring

The AHETF has SOPs related to subject safety and monitoring weather conditions to avoid heat-related illness (SOP 11.G., 11.N). The protocol originally referenced SOP 11.G. and was amended to also reference SOP 11.N. (AHE500 Study Report, pp. 490-491) These SOPs were followed during the study to minimize the risks of heat-related illness. All researchers were trained to recognize the symptoms of heat-related illness, a medical professional (nurse, certified first responder, or emergency medical technician) was on-site for each monitoring event and checked subjects for signs of heat-related illness. Observers closely watched subjects, reminded them to take breaks as necessary, and offered fluids. Tables CSLL-NR-7 and CSLL-R-7 summarize the weather conditions, including heat index, during each MU. There were no reports of heat-related illness during this study and no MUs were stopped because the heat index cutoff was reached.

Risk Minimization

The protocol identified several risks to subjects, including heat-related illness, scripting field activities, psychological risks, and exposure to surfactants and surrogate chemicals. All risks to subjects were appropriately minimized in accordance with precautions outlined in the protocol during the conduct of the study.

Respect for Subjects

Respect for subjects was demonstrated in several ways in the conduct of Study AHE500. First, subjects' privacy was maintained in accordance with the steps outlined in the protocol. SOPs AHETF-6.B, 6.D., 11.B, 11.D, and 11.J were followed. The subjects' identities were not revealed in the report or any other materials provided to EPA.

Subjects were free to withdraw from the study. In accordance with the protocol, subjects were reminded at several points (consent presentation, consent form signing, initiation of MU) that they were free to withdraw at any time without forfeiting any benefits or jeopardizing their employment. No subjects withdrew from the study, but several did choose not to proceed with a consent meeting after attending a recruitment meeting.

Subject Compensation

The protocol indicated that subjects would be compensated $20 for attending a consent meeting and $80 for participating in a monitoring event. The AHETF confirmed that all persons who participated in a consent meeting received $20, and that all 36 workers who were dressed for a monitoring event were compensated $80.

Employers were reimbursed by AHETF for the test substance that was handled by the study

participant.

Provision of Personal Exposure Results to Subjects

The protocol, consent form, and AHETF SOP 11.J., all indicate that subjects may request their personal study results. The AHETF noted that of the 36 subjects who were monitored, 32 requested their personalized monitoring results.

Protocol Amendments and Deviations

The protocol was amended 3 times and 6 deviation reports that included multiple deviations were made to the overseeing IRBs. This section discusses the amendments and deviations related to the ethical conduct of the study. It also discusses a discrepancy between the effective dates and the IRB-approval dates for some amendments, along with EPA's recommendations for future studies.

Amendment 1 revised the protocol to allow for heat stress management using the "wet bulb/globe/dry bulb temperature (WBGT) method as described in SOP AHETF-11.N.0." (AHE500 Study Report, pp. 490-491 of 1386). This amendment allowed for an additional method for ensuring subjects' safety when the heat index reached levels of concern. This amendment did not adversely impact subjects' safety or welfare.

Amendment 2 added an additional active ingredient (chlorpyrifos) to the list of surrogate chemicals that could be used in the study (AHE500 Study Report, pp. 492-493 of 1386). This protocol amendment did not include a corresponding edit to the consent materials, which also list all potential surrogate chemicals. Neither the AHETF nor the overseeing IRB caught the error during the amendment submission and approval process. Chlorpyrifos was not used during any of the monitoring events for the study, so there was no risk to subjects from the oversight in updating the consent form. This amendment did not adversely impact the subject's safety or welfare.

Amendment 3 included 3 parts. First, it revised the protocol and consent forms to specify that subjects must be trained as a handler in accordance with the Worker Protection Standard or exempt from requiring such training. This amendment was made based on conversations between EPA and AHETF about another study that raised the need clarify the protocol and consent materials to ensure that subjects were properly trained and qualified to perform the tasks being monitored. Second, the protocol and consent form were revised to add to the consent process and pre-monitoring discussion related to the labeling of the pesticide being used a note that the researcher would discuss with the subject "pertinent sections of the Directions for Use". (AHE500 Study Report, pp. 495 of 1386) This was added to ensure that subjects were familiar with the product's label and use directions prior to the monitoring event, even if the product was not known at the time of the consent meeting. (AHE500 Study Report, pp. 494-5 of 1386) Lastly, the amendment allowed the final 3 MUs to be collected in any of the monitoring areas. This change was made because there were recruiting difficulties delaying the collection of the final 3 MUs, despite expanding the original monitoring areas to adjacent locations. Ultimately, 3 MUs were collected in each of the monitoring areas. No aspect of this amendment adversely impacted subjects' safety or welfare.

The AHETF reported six protocol deviations (AHE500 Study Report, pp. 501-11 of 1386), some of which were related to subject health and safety and will be discussed here.

A deviation occurred in September 2013 when a subject (MU M9), who was an employee of a pesticide registrant, was enrolled in the study and participated in monitoring contrary to the study's eligibility criteria. (AHE500 Study Report, p. 501 of 1386) This occurred because the subject indicated during recruitment that the worked for an independent company, but at some point prior to

the monitoring event the company was sold to Wilbur-Ellis, a pesticide manufacturer. There was no indication that the subject's decision to participate was influenced at all by the new owner. In addition, Wilbur-Ellis is not a member of the AHETF. This deviation did not adversely affect the subject's safety or welfare.

A deviation occurred in May 2014 when a subject (MU M12) ate before having a face/neck wipe performed. (AHE500 Study Report, pp. 502-3 of 1386) This occurred because the subject indicated that he was going to smoke. Researchers performed a hand wash in accordance with the protocol. However, the subject then decided to eat during the break without indicating this to the researchers. The subject did not experience any adverse effects and there was no negative impact on the study.

A deviation occurred in June 2016 when a subject (MU M31) participated in monitoring without being trained as a handler under the Worker Protection Standard. The subject was working under the direct supervision of a certified applicator. This deviation occurred because the researcher obtaining consent believed that the subject's position made him exempt from the Worker Protection Standard training requirements. However, the regulation only exempts certified applicators from training, not those working under their direct supervision. Following this deviation, AHETF completed protocol amendment 3, which clarified the need for subjects to be trained under the Worker Protection Standard. The subject did not experience any adverse effects as a result of this deviation and there was no negative impact on the study.

A deviation occurred in October 2016 when a subject (MU M36) removed his chemical-resistant gloves for a short period during the MU in order to transfer the spray mixture from the mix tank to the application equipment. Researchers notified the subject during the monitoring event that chemical-resistant gloves should be worn, but the subject indicated that it was his usual practice to remove gloves for transferring the pesticide and that he was choosing to do so despite feedback from the researchers. The subject had his gloves off for a short period. The labeling and regulations do not require pesticide users to wear gloves when using a closed system to transfer certain types of products, including those being used during this MU. The Study Director followed up with the subject after the MU to discuss the event and explain when gloves are required, and submitted an unanticipated problem report to the IRB. The short duration of the event, use of a closed system, and relatively low toxicity of the chemicals support a conclusion that failure to wear gloves posed little to no additional risk to the subject. The subject did not report any adverse effects and the study results were not compromised by this deviation.

A deviation occurred throughout the conduct of the study and was reported twice, in deviations 4 and 6. The protocol noted that:

> *Prior to use in the study, the closed system and mixing/loading procedures shall be evaluated and discussed by the Study Director or a designated researcher to ensure the system is operating properly and the anticipated procedures do not involve open-pouring. This examination will include ensuring no significant leaks; discussing how connections will be made between containers and closed systems and between systems and hoses or tanks; and ensuring the system meets one of the four system types discussed above.* (AHE500 Study Report, pp. 474-5 of 1386)

Deviations 4 and 6 note that this failure to conform to the protocol occurred because "it was often not possible to see the system in operation, for example to verify there were no significant leaks." (AHE500 Study Report, p. 510 of 1386) The report notes that although pre-use inspections

were not done in all instances, researchers made note of leaks in their observation reports from the MUs and asked subjects whether leaks could be fixed and to do so early in the course of the MU. Some leaks could not be stopped and were contained by placing a bucket or cloth under the leak. The report indicates that the impact of these deviations was minimal to moderate, and that there were no reported incidents of overexposure to the test substances or adverse effects reported by subjects. It was not immediately apparent that these systems were leading to increased exposure to the subjects, such that an MU or the entire study should be stopped.

Closed systems are engineering controls designed to reduce worker exposure to pesticides while loading them into application equipment and preparing tank mixes when they are operating properly. Labeling and regulation also allow workers to reduce PPE worn in some instances (e.g., no gloves required when transferring pesticides with certain signal words through a closed system). Failure to inspect the equipment prior to the start of MUs could have had an impact on subjects' safety and welfare if they were using a malfunctioning system. However, during this study subjects were using equipment with which they were familiar and that they (or their employers) considered closed systems, and would likely be using the equipment in the same condition regardless of their participation in the study. The data collected provide valuable real-world information about subjects' exposure, and appears to not have impacted subjects' safety or welfare. In the future, EPA recommends that when AHETF encounters a situation where they cannot follow the protocol, they consult with EPA before deviating from the protocol requirements for the duration of the study.

Protocol Amendment Submission & IRB Approval Dates

The EPA noted an issue related to amendment approval dates. The effective dates of some amendments predate the IRB's approval of the amendments. For example, Amendment 1's effective date is listed as April 16, 2014 (AHE500 Study Report, p. 490 of 1386). However, the IRB did not approve the amendment until April 17, 2014. (AHE500 IRB Correspondence Report, p. 492 of 891). Amendment 2 lists the effective date as May 4, 2015 (AHE500 Study Report, p. 492 of 1386, but the IRB did not approve the amendment until May 5, 2015 (AHE500 IRB Correspondence Report, p. 568 of 1386). The discrepancies in the effective dates on the study did not affect subject safety or welfare; however, amendments are not effective until the IRB has reviewed and approved them. The EPA recommends that in future studies, the effective dates of amendments be listed as "IRB approval date" or left blank at the time of submission to the IRB and added after IRB approval.

Applicable Ethical Standards

The following provisions of 40 CFR 26 Subpart Q define the applicable ethical standards which read in pertinent part:

> **§26.1703**: Except as provided in §26.1706, EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1705**: Except as provided in §26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are

reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Prohibition of research involving intentional exposure of pregnant or nursing women or of children

40 CFR §26.1703 prohibits research involving intentional exposure of pregnant or nursing women or of children under 18. All subjects who participated in study AHE500 were at least 18 years old. With subject screening and pregnancy testing on the day of monitoring, the AHETF confirmed that no female subjects were pregnant or lactating. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. Based on available information submitted by AHETF to EPA, study AHE500 was conducted in substantial compliance with subparts K and L.

Compliance with 40 CFR §26 subpart M

As documented in Attachment 2 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

Compliance with FIFRA §12(a)(2)(P)

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable therefrom," and "freely volunteer to participate in the test," was met for this study.

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AHE500 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. From EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research will also undergo review by the HSRB.

cc: Rick Keigwin
Dana Friedman
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Attachment 1: EPA and HSRB ethics-related comments on protocol & AHETF responses
Attachment 2: §26.1303 Completeness checklist for AHE500 Study

Attachment 1
Ethics Comments from October 2011 HSRB Meeting & AHETF Actions

EPA Comments on AHE500 Protocol	AHETF Actions to Address Comments
Add a statement to the consent form that explains to subjects that if, after their participation in the study, they experience symptom that they believe is related to their participation in the study, they should contact the Study Director immediately. A telephone number should be provided.	The final IRB-approved consent form includes a 24-hour telephone number and email address for the study director, as well as a toll-free 24-hour number that would reach the Study Director/Study Sponsor, with instructions to call "if at any time you think you have a research-related injury or illness". Additionally, they added a line to include the number to call for medical emergencies involving the product handled. (AHE500 IRB Correspondence Report, pp. 221-231)
Develop procedures for handling such a call and document those procedures in a new or existing SOP.	The protocol references SOPs AHETF-11.H. and 11.J, which note that the subjects will be reminded at the end of the monitoring period of the number to call if any study-related illnesses or injuries become apparent after the study participation is completed, and that the Study Director will consult with the on-call medical professional in order to make a determination of what course of action should be taken.
HSRB Comments on AHE500 Protocol	**AHETF Actions to Address Comments**
The Board concurred with the Agency's recommendation that an SOP needs to be developed that specifies the criteria by which study investigators will decide that a participant is "too sick to make a decision about getting medical treatment".	SOP AHETF-11.H was revised to include the following: *The study participant (worker) may refuse medical treatment unless the medical professional decides the worker is not competent to make a decision about getting medical treatment. In order to refuse treatment, the participant must be able to do all the following: a) appreciate the situation and its consequences; b) understand the relevant information; c) reason about the treatment decision; and d) communicate a choice (see Appelbaum, P.S. Assessment of Patients' Competence to Consent to Treatment. N Engl J Med 2007; 1834-1840. November 1, 2007)* See AHETF SOP Manual 12JAN2015 EPA Version, p. 175.
If AHETF elects to provide personal monitoring results to subjects in Study AHE500, consult resources developed by the HSRB.	AHETF elected to offer subjects the opportunity to receive their personal monitoring results. The letter was drafted to provide the subjects with relevant information in a readable and user-friendly manner.